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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,966	04/16/2004	James McSwiggen	03-465-D (400/151)	2134

65778 7590 09/25/2007

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
09/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,966	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,14-21,30,31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 14-21, 30, 31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on September 2, 2007 has been entered.

Claims 1, 3, 14-21, 30, 31 and 33 have been amended.

Claims 1, 3, 14-21, 30, 31 and 33 are pending in the instant application.

Claims 1, 3, 14-21, 30, 31 and 33 have been examined on the merits.

Response to Arguments

Applicant's Amendment and Response mailed September 2, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed June 8, 2007 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Priority

The instant claims, drawn to a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein

each strand is about 18 to about 27 nucleotides in length; the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674; the sense strand is complementary to the antisense strand; and about 100% of the nucleotides in one or both strands are chemically modified have been afforded priority to U.S. Provisional 60/358,580 filed February 20, 2002.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 14-21, 30, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number AF100308 (submitted and made of record on the information disclosure statement filed August 13, 2004), in view of U.S. Patent No. 5,985,662 ('662), Hammond et al. (Nature Genetics 2001, Vol. 2:110-119), Elbashir et al. (EMBO Journal, 2001 Vol. 20:6877-6888, submitted and made of record on Applicant's information disclosure statement filed August 13, 2004), Matulic-Adamic

et al. (US Patent No. 5,998,203), and Parrish et al. (submitted and made of record on Applicant's information disclosure statement filed August 13, 2004).

Applicant is reminded that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. The term "about" has not been defined in the instant specification, therefore, the Examiner is interpreting the limitation, "about 100%" broadly to be at least 50%.

Applicant is also reminded that the instant application has been afforded priority to the filing date of U.S. Provisional 60/358,580 filed February 20, 2002. For further explanation, see the discussion above under the heading "Priority".

Claim 1 is drawn to a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length; the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674; the sense strand is complementary to the antisense strand; and about 100% of the nucleotides in one or both strands are chemically modified. Claims 3, 14-21, 30, 31 and 33 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein said siRNA molecules comprise one or more ribonucleotides; wherein one or more purine or pyrimidine nucleotides are present on the sense strand; wherein the purine nucleotide is a 2'-deoxy purine and the pyrimidine nucleotide is a 2'-deoxy-2'-fluoro pyrimidine nucleotide; wherein the sense strand comprises a terminal cap moiety at the 5' or 3' end, or both; wherein said terminal cap moiety is an inverted deoxy abasic moiety; wherein the antisense strand comprises 2'-deoxy-2'-fluoro pyrimidine nucleotides;

wherein the purine nucleotide on the antisense strand is a 2'-methyl purine nucleotide or a 2'-deoxy purine nucleotide; wherein the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand; wherein the 5'-end of the antisense strand includes a terminal phosphate group; and a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length; the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674; the sense strand is complementary to the antisense strand; and about 100% of the nucleotides in one or both strands are chemically modified in a pharmaceutically acceptable carrier or diluent.

GenBank Accession Number AF100308 teaches the sequence of a human hepatitis B virus (HBV).

GenBank Accession Number AF100308 does not teach a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein each strand is about 18 to about 27 nucleotides in length; the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674; the sense strand is complementary to the antisense strand; and about 100% of the nucleotides in one or both strands are chemically modified.

'662 teach and claim antisense phosphorothioate oligodeoxynucleotides targeted to HBV (see Table 1 and claim 2). 662' teaches at columns 6 and 7, that oligonucleotides with chemical modifications are useful because of their resistance to

nucleases.

Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. For example, on page 110, first column, Hammond teaches that antisense methods are straightforward but suffer from "questionable specificity and incomplete efficacy". RNA interference on the other hand, "has been shown in diverse organisms to inhibit gene expression in a sequence-specific manner" (same page and column) and requires only a few molecules of dsRNA per cell to silence expression. Hammond also teaches that the RNA interference phenomenon in animals was discovered by researchers who were using antisense techniques and found that the use of double stranded instead of single-stranded RNAs reduced gene expression tenfold more efficiently (see paragraph bridging pages 110-111).

Elbashir et al. teach RNA interference (RNAi) is a newly discovered pathway of inhibiting gene expression by using an antisense-like mechanism. Specifically, Elbashir et al. teach short interfering RNAs (siRNAs) as mediators of RNAi and inhibitors of gene expression. Detailed protocols and methods are provided for designing, preparing, testing, and using siRNA to silence/inhibit expression of virtually any known gene. Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). Elbashir et al. teach that duplexes, 21 nucleotides in length, with 2 nt 3' overhangs, were the most efficient

triggers of sequence-specific mRNA degradation. Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see Figures 7 and 8). Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function. Elbashir et al. also teach siRNA duplexes were incubated in a *D.melanogaster* RNAi/translation reaction for 15 min prior to addition of mRNAs, where the reaction mixture constitutes a pharmaceutically acceptable carrier or diluent. Elbashir et al. also teach complete substitution of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate extensive substitutions/chemical modifications to a siRNA to determine overall RNAi activity.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures (see Abstract). The double stranded nucleic acid RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the double stranded nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate

modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications (see Figure 5). One or both strands comprise modifications. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the RNA interference process (see Summary).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense wherein the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674 using the sequence taught by GenBank Accession Number AF100308, the motivation of '662 and Hammond et al., and following the methods of Elbashir et al., Matulic-Adamic et al., and Parrish et al. It would have been obvious to have about 100% of the nucleotides in one or both strands be chemically modified using the teachings and motivation of Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. It would have been obvious to have the siRNA comprised in a

pharmaceutically acceptable carrier or diluent using the teachings and motivation of Elbashir et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to incorporate about 100% of the purine nucleotides in one or both stands of the siRNA be 2'-O-methyl purine nucleotides and about 100% of the pyrimidine nucleotides in one or both strands of the siRNA be 2'-deoxy-2'-fluoro pyrimidine nucleotides to determine the tolerance of chemical modifications for RNAi activity as taught by Elbashir et al. It would have been obvious to incorporate a terminal cap moiety on one of the ends of the sense strand since Matulic-Adamic et al. taught such modifications protect the nucleic acid from exonuclease degradation. It would have been obvious to incorporate a phosphorothioate internucleotide linkage at the 3' end of the antisense strand or a terminal phosphate group at 5'-end of the antisense strand since either Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. teach such modifications protect the nucleic acid from nuclease attack.

It would have been *prima facie* obvious to one of ordinary skill in the art to substitute the antisense phosphorothioate oligodeoxynucleotides complementary to HBV taught by '662 with the chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense as instantly claimed because the substitution of one known element for another would have yielded predictable results at the time of the invention.

One of ordinary skill in the art would have been motivated to make a chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and

an antisense wherein the antisense strand is complementary to a portion of a Hepatitis B Virus (HBV) RNA encoded by SEQ ID NO:674 since '662 taught the desirability of using nucleic acid inhibitors of gene expression to inhibit HBV for use as a potential therapy for patients infected with HBV. One would have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications into the chemically synthesized siRNA since these modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid (see Elbashir et al., Matulic-Adamic et al., and Parrish et al.). It was well known in the art at the time of filing to incorporate one or more modifications, including 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications, into oligonucleotides, as evidenced by Elbashir et al., Matulic-Adamic et al., and Parrish et al. Elbashir et al. demonstrated both 2'-deoxy and 2'-O-methyl modifications of double stranded oligonucleotides at the time the invention was made. Matulic-Adamic et al. taught double stranded oligonucleotides comprising more than one specific type of modification. Additionally, Parrish et al. teach various modifications to double stranded duplexes and teach that different modifications are tolerated at different locations of the duplex. Elbashir et al. and Parrish et al. demonstrate the routine nature of testing various chemical modifications for optimization and stabilization of a double stranded duplex. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a double stranded nucleic acid molecule, such as a siRNA in order to stabilize and optimize

delivery of the nucleic acid. One of skill in the art would be motivated to incorporate chemical modifications to about 100% of the nucleotide positions in one of the strands of the nucleic acid molecule to test the overall effect on RNAi activity as taught by Elbashir et al. One of skill in the art would be motivated to have the siRNA comprised in a pharmaceutically acceptable carrier or diluent to facilitate its delivery *in vitro* as taught by Elbashir et al.

One of ordinary skill in the art would have been motivated to substitute the antisense phosphorothioate oligodeoxynucleotides complementary to HBV taught by '662 with the chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense as instantly claimed since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. For further discussion, see the post-filing reference of Scanlon, KJ (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420).

There would be a reasonable expectation of success to apply each of the claimed modifications to the siRNA molecules of the claimed invention because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. There would be a reasonable expectation of success to apply chemical modifications to about 100% of the nucleotide positions in one or both strand(s) of the siRNA molecule since Elbashir et al. taught the design of such nucleic acids was known to be successful in the art at the time the invention was made. Therefore, one would reasonably expect for such

modifications to benefit the siRNA as instantly claimed.

One of ordinary skill in the art would have expected success at substituting the antisense phosphorothioate oligodeoxynucleotides complementary to HBV taught by '662 with the chemically modified double stranded short interfering RNA (siRNA) comprising a sense strand and an antisense as instantly claimed because the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information

for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
September 20, 2007

/Terra Cotta Gibbs/